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Description

[0001] The present invention relates to novel pyridine derivatives and, more particularly, to novel N-(2-pyridyl) sulphonamides, and pharmaceutically-acceptable salts thereof, which possess endothelin receptor antagonist activity. These compounds are of value whenever such antagonist activity is desired, such as for research tools within pharmacological, diagnostic and related studies or in the treatment of diseases or medical conditions including, but not limited to, hypertension, pulmonary hypertension, cardiac or cerebral circulatory disease and renal disease, in warm-blooded animals (including man), in which elevated or abnormal levels of endothelin play a significant causative role. The invention also relates to pharmaceutical compositions of the novel compounds (and their salts) for use in treating said diseases or medical conditions, and to processes for the manufacture of the novel compounds. The invention further relates to the use of the novel compounds in treating one or more of the said diseases or medical conditions. A method of treating one or more of the said diseases or medical conditions using said compounds is also provided.

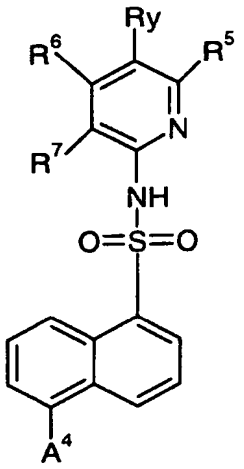
[0002] The endothelins are a family of endogenous 21 amino acid peptides comprising three isoforms, endothelin-1, endothelin-2 and endothelin-3. The endothelins are formed by cleavage of the Trp^{21}-Val^{22} bond of their corresponding proendothelins by a putative endothelin converting enzyme. The endothelins are among the most potent vasoconstrictors known and have a characteristic long duration of action. They exhibit a wide range of other activities including cell proliferation and mitogenesis, extravasation and chemotaxis, and also interact with a number of other vasoactive agents. They also have direct effects on the heart. Thus the biological profile of the endothelins is consistent with a pathophysiological role in the cardiovascular system. The endothelins also have actions on other physiological systems including the airways, gastro-intestinal tract, reproductive system, kidney, liver, central nervous system, neuro-endocrine system and the blood.

[0003] The endothelins are released from a range of tissue and cell sources including vascular endothelium, vascular smooth muscle, kidney, liver, uterus, airways, intestine and leukocytes. Release can be stimulated by hypoxia, shear stress, physical injury and a wide range of hormones and cytokines. Elevated endothelin levels have been found in a number of disease states in man including hypertension, pulmonary hypertension, pre-eclampsia, congestive heart failure, myocardial infarction, angina pectoris, acute and chronic renal failure, ischaemic stroke, subarachnoid haemorrhage, atherosclerosis, hypercholesterolaemia, cardiogenic and endotoxic shock, diabetes mellitus, Raynaud's disease, scleroderma, systemic sclerosis, Buerger's disease, rheumatoid arthritis, asthma, bronchitis, acute respiratory failure, liver cirrhosis, Crohn's disease, ulcerative colitis, certain cancers and after surgery.

[0004] Japanese patent application 61/257960 describes certain related sulphonamides having fungicidal activity, the compounds N-(5-chloro-2-pyridyl)-2-naphthalenesulphonamide, N-(5-chloro-2-pyridyl)-1-naphthalenesulphonamide, N-(5-trifluoromethyl-2-pyridyl)-2-naphthalenesulphonamide and N-(5-trifluoromethyl)-1-naphthalenesulphonamide being specifically described. International patent application no. 90/09787 discloses certain related sulphonamides as radiosensitizers and/or chemosensitizers. J. Indian Chem. Soc., Vol 46, No. 2, 1969, 115 to 118 and Vol 46, No. 5, 1969, 411-414 disclose certain N-(2-pyridyl)naphthalenesulphonamides which were screened for antibacterial activity. In European patent applications, publication nos. 558258 and 569193 are described certain N-(isoxazolyl) sulphonamides which are referred to as endothelin receptor antagonists.

[0005] Although a number of endothelin receptor antagonists are known, there is a continuing need for alternative antagonists. The present invention is based in part on this need and on our discovery of the unexpected antagonism of the endothelin receptor by certain N-heterocyclyl sulphonamides.

[0006] According to one aspect of the invention there is provided a compound of the formula Ia



Ia

wherein
Ry is selected from halogeno, (1-4C)alkyl, trifluoromethyl and nitro; A^4 is selected from:-

(i) (1-4C)alkanoylamino;
(ii) the group -NRaRb in which Ra and Rb are the same and are selected from methyl, ethyl and propyl;
(iii) the group -NRaRb in which one of Ra and Rb is methyl and the other is ethyl or propyl; and
(iv) the group -NRaRb in which one of Ra and Rb is hydrogen and the other is methyl, ethyl, propyl, isopropyl, isobutyl or sec-butyl; and R^5, R^6 and R^7 are independently selected from hydrogen, halogeno, (1-4C)alkoxy and (1-4C)alkyl; or a pharmaceutically-acceptable salt thereof.

[0007] It will be appreciated that, depending on the nature of the substituents, certain of the formula Ia compounds may possess one or more chiral centres and may be isolated in one or more racemic or optically active forms. It is to be understood that the present invention concerns any form of such a compound of formula Ia which possesses the afore-mentioned useful pharmacological properties, it being well known to make optically active forms, for example by synthesis from suitable chiral intermediates or by resolution, and how to determine their pharmacological properties, for example by use of the tests described hereinafter.

[0008] It will also be appreciated that a compound of formula Ia may exhibit polymorphism, that a compound of formula Ia may form a solvate and that a compound of formula Ia may exist in more than one tautomeric form. It is to be understood that the present invention also concerns any polymorphic form, any tautomer or any solvate, or any mixture thereof, which possesses endothelin receptor antagonist activity.

[0009] It is further to be understood that generic terms such as "alkyl" include both straight and branched chain variants when the carbon numbers permit.

[0010] However, when a particular radical such as "propyl" is given, it is specific to the straight chain variant, branched chain variants such as "isopropyl" being specifically named when intended. The same convention applies to other radicals.

[0011] Particular values for A^4, Ry, A^5, R^6 or R^7 where appropriate include, by way of example,

for (1-4C)alkyl: methyl, ethyl, propyl, isopropyl and sec-butyl;
for (1-4C)alkoxy: methoxy, ethoxy, propoxy, isopropoxy and butoxy;
for halogeno: fluoro, chloro, bromo and iodo; and
for (1-4c) alkanoylamino: formamido, acetamido and propionamido;

[0012] A value for Ry which is especially preferred is halogeno.

[0013] A sub-group of values for R^5, R^6 or R^7 of particular interest include especially hydrogen, methyl, chloro and bromo.

[0014] A preferred value for the naphthyl ring bearing A^4 includes, for example, 5-N,N-di(1-4C)alkylaminonaphth-1-yl, such as 5-dimethylaminonaphth-1-yl.

[0015] Compounds in which A^4 is, for example, the group -NRaRb in which Ra and Rb have any of the meanings

defined hereinbefore (such as dialkylamino, for example dimethylamino) are preferred.

[0016] Groups of compounds of the invention of particular interest include, for example, compounds of the formula Ia wherein A^4 is selected from

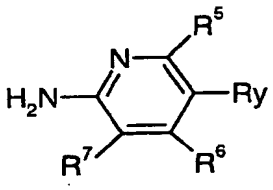
(i) acetylamino;
(ii) the group -NRaRb in which Ra and Rb are the same and are methyl;
(iii) the group -NRaRb in which one of Ra and Rb is methyl and the other is ethyl or propyl; and
(iv) the group -NRaRb in which one of Ra and Rb is hydrogen and the other is ethyl or isopropyl; and
R^5, R^6 and R^7 have any of the meanings defined hereinbefore.

[0017] Compounds of the invention which are of particular interest include, for example, the specific embodiments set out hereinafter in the accompanying Examples. Of these, the compounds of formula Ia disclosed in Examples 1, 3, 6 and 7 are of special interest and these compounds, or a pharmaceutically-acceptable salt thereof, are provided as a further feature of the invention.

[0018] Suitable pharmaceutically-acceptable salts include, for example, salts with alkali metal (such as sodium, potassium or lithium), alkaline earth metals (such as calcium or magnesium), ammonium salts, and salts with organic bases affording physiologically acceptable cations, such as salts with methylamine, dimethylamine, trimethylamine, piperidine and morpholine. In addition, for those compounds which are sufficiently basic suitable pharmaceutically-acceptable salts include, pharmaceutically-acceptable acid-addition salts with hydrogen halides, sulphuric acid, phosphoric acid and with organic acids such as citric acid, maleic acid, methanesulphonic acid and p-toluenesulphonic acid. Alternatively, the compound of formula Ia may exist in a zwitterionic form.

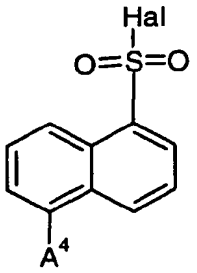
[0019] The compounds of formula Ia may be obtained by standard procedures of organic chemistry well known in the art for the production of structurally analogous compounds. Such procedures are provided as a further feature of the invention and include, by way of example, the following procedures in which the generic radicals have any of the values given above, unless stated otherwise.

(a) an amine (or an alkali metal salt thereof) of the formula II:



II

is reacted with a sulphonyl halide of formula III:



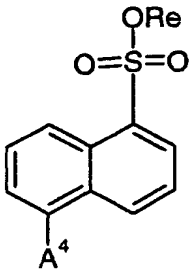
III

in which Hal. is a halogeno group (for example, chloro, bromo or iodo) in a suitable solvent.

[0020] A suitable solvent includes, for example, pyridine. A catalyst, such as 4-dimethylaminopyridine or 4-pyrrolidinopyridine, may be added to assist the coupling reaction. The reaction is generally carried out at a temperature in the range of, for example, 0°C to 120°C and more generally 20°C to 120°C. Alternatively a solvent such as dichloromethane, chloroform, dimethoxyethane, tetrahydrofuran or dioxan may be used in the presence of a suitable inorganic base, such as sodium or potassium carbonate (which may be present as an aqueous solution) or an organic base, for example a tertiary amine such as pyridine or triethylamine. When the alkali metal salt of the amine of formula II is used, this may be formed, for example, with the use of a suitable base such as lithium diisopropylamide at a temperature, for

example, about -60°C, or sodium hydride, for example, at ambient temperature, prior to the addition of the sulphonyl halide. However it will be appreciated that the reaction of a sulphonyl halide with an amine to form a sulphonamide (and the type of solvents and conditions used therein) is well-known in the art.

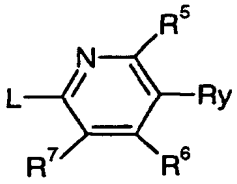
[0021] Alternatively an amine (or alkali metal salt thereof) of the formula II may be reacted with a sulphonate of the formula IIIa:



IIIa

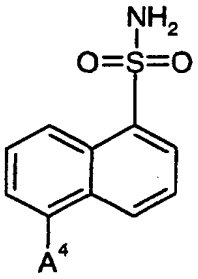
in which Re is an electron deficient phenyl group, for example a phenyl group bearing one or more electron withdrawing groups, such as nitro or cyano, in a suitable solvent. A preferred value for Re includes, for example, 4-nitrophenyl. The reaction is carried out under similar conditions to those described above.

(b) a compound of the formula IV:



IV

in which L is a suitable leaving group (such as chloro, bromo, iodo, methanesulphonyloxy or p-toluenesulphonyloxy) is reacted with a sulphonamide of the formula V.



V

The reaction is generally carried out in the presence of a base, such as an alkali metal alkoxide (such as sodium methoxide, potassium methoxide, sodium ethoxide or potassium ethoxide) or an alkali metal hydride (such as sodium or potassium hydride), or an organic base such as diisopropylethylamine. The reaction may also be carried out using a pre-formed alkali metal salt of a compound of the formula V.

[0022] A suitable inert organic solvent is usually employed, for example, N,N-dimethylformamide or N-methylpyrrolidone. The reaction is generally carried out at a temperature in the range of, for example, 20°C to 120°C.

[0023] Sulphonyl halides of formula III are well known in the art or may be obtained, for example, by the procedures

described in European patent application, publication no. 558258 and 569193, or by analogy therewith. They may also be obtained by reaction of an appropriate naphthylamine with sodium nitrite and hydrochloric acid to form a diazonium salt, followed by reaction of the diazonium salt with sulphur dioxide in dioxan and work-up with a haloacid. Compounds of the formula IIIa may be obtained from the corresponding sulphonyl chloride by reaction with the appropriate phenol (Re.OH) using conventional procedures, for example, by heating in pyridine. Compounds of formula II and IV are commercially available or are also well-known in the art, being described in standard works of heterocyclic chemistry such as those edited by Elderfield or Wiessberger, and others can be obtained by analogy therewith using standard procedures of organic chemistry. The sulphonamides of formula V may be obtained from corresponding compounds of formula III using standard procedures.

[0024] Whereafter, a compound of the formula Ia may be converted into another compound of the formula Ia by conventional functional group interconversion. It will be appreciated that it may be necessary to protect one or more functional groups with a suitable protecting group prior to carrying out the process of (a) or (b) above, or prior to carrying out a functional group interconversion, followed by removal of the protecting group. Suitable protecting groups and procedures for their use, together with procedure for removing the protecting group, are well known in the art, for example as described in "Protective Groups in Organic Syntheses" by Theodora Green (John Wiley and Sons Inc., 1981).

[0025] Whereafter, when a pharmaceutically-acceptable salt of a compound of formula Ia is required, it may be obtained, for example, by reaction with the appropriate base affording a physiologically-acceptable cation, or with the appropriate acid affording a physiologically-acceptable amine, or by any other conventional salt formation procedure.

[0026] Further, when an optically active form of a compound of formula Ia is required, one of the aforesaid processes may be carried out using an optically active starting material. Alternatively, the racemic form of a compound of formula Ia may be resolved, for example by reaction with a optically active form of a suitable organic base, for example, ephedrine, N, N, N-trimethyl(1-phenylethyl)ammonium hydroxide or 1-phenylethylamine, followed by conventional separation of the diastereoisomeric mixture of salts thus obtained, for example by fractional crystallisation from a suitable solvent, for example a (1-4C)alkanol, whereafter the optically active form of said compound of formula Ia may be liberated by treatment with acid using a conventional procedure, for example using an aqueous mineral acid such as dilute hydrochloric acid.

[0027] As stated above, the compounds of formula Ia will have beneficial pharmacological effects in warm-blooded animals (including man) in diseases and medical conditions where elevated or abnormal levels of endothelin play a significant causative role. (References to studies supporting the implication of endothelin in various diseases or medical conditions are, for example, disclosed in International Patent Applications, Publication Nos. WO 93/21219 and WO 94/02474.) The compounds of the invention will thus be useful in the treatment of diseases or medical conditions such as hypertension, pulmonary hypertension, congestive heart failure, dyslipidaemia, atherosclerosis, restenosis, acute and chronic renal failure, ischaemic stroke, subarachnoid haemorrhage, intermittent claudication, critical limb ischaemia, asthma, and organ failure after general surgery or transplantation. They may also be useful for the treatment of pre-eclampsia, premature labour, myocardial infarction, angina pectoris, dysrrhythmia, cardiogenic and endotoxin shock, diabetes mellitus, Raynaud's disease, scleroderma, Buerger's disease, systemic sclerosis, bronchitis, acute respiratory distress syndrome, liver cirrhosis, osteoporosis, Crohn's disease, ulcerative colitis, irritable bowel syndrome, urinary incontinence, migraine, glaucoma and arthritis.

[0028] A further feature of the present invention is the use of a compound of the formula Ia, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of one or more of the aforesaid diseases or medical conditions.

[0029] The endothelin receptor antagonist activity of the compounds of the invention may be assessed using one or more of the following procedures:

[0030] Test A: The endothelin receptor antagonist activity of compounds of formula I may be assessed in vitro by their ability to inhibit binding of [^{125}I]-Endothelin-1 to its receptors. Human ET_A or ET_B receptors (sub-types of the endothelin receptor) were expressed in Mouse Erythroleukemic Cells (MEL cells) by using standard molecular techniques (for example, as described by Sambrook J., Fritsch E.F. & Maniatis T. (1989) Molecular Cloning: A Laboratory Manual, 2nd Edition, Cold Spring Harbor Press, USA). cDNA sequences encoding the human ET_A and ET_B receptor (Hosoda K. et al (1991), FEBS Lett., 287, 23-26 and Sakamoto A. et al, (1991), Biochem. Biophys Res. Comm., 178, 656-663) are subcloned into pBluescript vector followed by insertion into the MEL cell expression vector pEV as described by Needham et al (1992), Nuc. Acids Res., 20, 997-1003. The resultant expression vector was transfected into MEL cells by electroporation using procedures described by Shelton et al., (1993), Receptors and Channels, 1, 25-37. MEL cells expressing the recombinant human ET_A or ET_B receptor were grown in Dulbecco's Modified Eagle's Medium (DMEM) with 10% Fetal Calf Serum (FCS), 1% glutamine, 1% penicillin/streptomycin and 2 mg/ml Gibco Geneticin (G-418) sulphate. After 3-6 days induction with 1% N,N-dimethylsulphoxide, the MEL cells were harvested for membrane preparation. Freshly prepared MEL cell pellets ($3x10^9$ cells) were homogenised in 30 ml of buffer containing 50mM 2-amino-2-(hydroxymethyl)-1,3-propanediol hydrochloride (Tris HCl), 0.19M sucrose, 5 µg/ml soybean trypsin

inhibitor, 100 µg/ml bacitracin, 1mM benzamidine and 1mM phenanthroline pH 7.4 at 5°C. Unbroken cells and nuclei were sedimented by centrifuging the homogenate at 1500 x g for 15 minutes at 5°C. The membrane pellet was resuspended in buffer and stored in liquid nitrogen until use.

[0031] [^{125}I]-Endothelin-1 binding to MEL cell membranes was measured in incubation buffer containing 50mM Tris HCl, 1mM $CaCl_2$, 0.05% polyoxyethylenesorbitan monolaurate, 0.1% Bovine Serum Albumin (BSA), 0.02% sodium azide pH 7.4 at 30°C after 180 minutes incubation. Membrane suspension (equivalent to 1.5µg and 0.5µg protein/tube ET_A and ET_B receptor respectively) was added to the incubation containing test compound and 30pM[^{125}I]-Endothelin-1 in a total volume of 225µl. Nonspecific binding was measured in the presence of 100nM unlabelled Endothelin-1. The incubation was terminated by harvesting the incubation with 50mM Tris pH 7.4 through a GF/B filter on a Brandel cell harvestor. The filter discs were punched out and counted in a gamma counter. Compounds are tested in triplicate over a range of concentrations and IC_{50} (or pIC_{50}) values calculated.

[0032] In general, compounds of formula Ia as defined above show inhibition in Test A at a concentration of about 10 micromolar or much less.

[0033] Test B: The endothelin receptor antagonist activity of compounds of formula Ia may be assessed in vitro in isolated tissues by their ability to inhibit the relaxant response to endothelin-1 in the guinea-pig isolated taenia coli. Guinea pigs of either sex and weight >250 g are killed by cervical dislocation and the caecum removed and placed in cold oxygenated Krebs solution. Strips of taenia coli are dissected out and approximately 4 cm lengths set up for isotonic recording in a 20 ml organ bath containing oxygenated Krebs solution at 32°C. After a 90-120 minute equilibration period to allow the tissue to spontaneously develop an increased tone, a cumulative concentration-response curve (relaxation) is constructed to endothelin-1 (0.3-10nM). The tissue is then washed for a period of at least 90 minutes before construction of a second concentration-response curve to endothelin-1 in the presence of the test compound. The test compound is added to the organ bath (at an initial concentration of 20µM) at least 30 minutes before constructing the second concentration-response curve to endothelin-1. The endothelin-1 concentration ratio for each experiment is determined by comparing the most parallel portions of the control and drug treated concentration-response curves. From this a pA_2 is calculated: pA_2 = -log[molar drug concentration] + log[concentration ratio - 1].

[0034] Test C: This in vivo test involves the measurement of the antagonist effect of the test compound against the pressor response induced by intravenously-administered proendothelin-1 in a pithed rat preparation.

[0035] Male rats (280-330g) are anaesthetised with halothane and artificially respired through a tracheal cannula. Rats are pithed by passing a 2mm diameter needle through the orbit, through the foramen magnum, and down into the spinal canal. The left femoral vein and the right carotid artery are isolated and catheters filled with heparinised saline are implanted for administration of compounds and measurement of blood pressure respectively. Body temperature is maintained at 38°C (as measured rectally) by a heated pad. Rats with an initial baseline mean arterial pressure of less than 55 mmHg or greater than 70 mmHg are excluded. Blood pressure is allowed to stabilize for approximately 10 minutes before a baseline reading is taken. Two initial challenges of proendothelin-1 (0.3 and 1.0 nmol kg^{-1}) are administered intravenously in a cumulative fashion and pressor responses recorded. Thereafter, a 55 minute recovery period is allowed and rats in which the blood pressure fails to return to within 20% of the baseline are excluded. Test compound is dosed intravenously at a dose volume of 1.0 ml kg^{-1} body weight and further challenges of proendothelin-1 are administered 5 minutes later. Proendothelin-1 is administered cumulatively in increasing doses (starting at 0.3 nmolkg^{-1}) until pressor responses are observed. Endothelin receptor antagonism is quantified by calculating dose ratio shifts at the 30mmHg change level.

[0036] Test D: This in vivo test involves the measurement of the antagonist effect of the test compound against the pressor response induced by intravenously-administered proendothelin-1 in a conscious rat preparation.

[0037] Male rats (260-290 g) are anaesthetised with Saffan administered via the tail vein. The right jugular vein and carotid artery are isolated and catheters filled with heparin implanted. These are exteriorised at the back of the neck using a metal trochar and the neck incision closed with autoclips. Rats are housed individually with free access to food and water during the recovery phase. Later in the day, food is removed and the rats are fasted overnight with free access to water. The following day the rats are placed in perspex restraining tubes and the arterial catheter drained and connected to a pressure transducer for measurement of mean arterial pressure. Following a ten minute stabilization period, proendothelin-1 (usually 0.3-1.0 nmol kg^{-1}) is administered cumulatively until a pressor response of 30 mmHg is achieved. The animals are then returned to their cages and allowed to recover for 2 hours. The test compound is administered orally (by gavage) at a known time point during the recovery period. The dose response curve to proendothelin-1 is then repeated at a fixed time after the oral dose (usually 0.5 or 1.0 hours) and again at a further time point (3 or 5 hours). Endothelin receptor antagonism is quantified by calculating dose ratio shifts at the 30mmHg change level.

[0038] By way of illustration of the endothelin receptor antagonist activity of compounds of the formula Ia, the compound of Example 6 gave the following results in tests A and B described above:

In test A: pIC_{50} 6.5
In test B: pA_2 6.6

[0039] The compounds of formula Ia will generally be administered for therapeutic or prophylactic purposes to warm-blooded animals (including man) requiring such treatment in the form of a pharmaceutical composition, as is well known in the pharmaceutical art. According to a further feature of the invention there is provided a pharmaceutical composition comprising a compound of formula Ia, or a pharmaceutically acceptable salt thereof as defined above, together with a pharmaceutically acceptable diluent or carrier. Such compositions will conveniently be in a form suitable for oral administration (e.g. as a tablet, capsule, solution, suspension or emulsion) or parenteral administration (e.g. as an injectable aqueous or oily solution, or injectable emulsion).

[0040] The compounds of formula Ia, or a pharmaceutically acceptable salt thereof, may also be advantageously administered for therapeutic or prophylactic purposes together with another pharmacological agent known in the general art to be of value in treating one or more of the diseases or medical conditions referred to hereinabove, such as beta-adrenergic blocker (for example atenolol), a calcium channel blocker (for example nifedipine), an angiotensin converting enzyme (ACE) inhibitor (for example lisinopril), a diuretic (for example furosemide or hydrochlorothiazide), an endothelin converting enzyme (ECE) inhibitor (for example phosphoramidon), a neutral endopeptidase (NEP) inhibitor, an HMGCoA reductase inhibitor, a nitric oxide donor, an anti-oxidant, a vasodilator, a dopamine agonist, a neuroprotective agent, a steroid, a beta-agonist, an anti-coagulant, or a thrombolytic agent. It is to be understood that such combination therapy constitutes a further aspect of the invention.

[0041] In general a compound of formula Ia (or a pharmaceutically acceptable salt thereof as appropriate) will be administered to man so that, for example, a daily oral dose of up to 50 mg/kg body weight (and preferably of up to 10 mg/kg) or a daily parenteral dose of up to 5 mg/kg body weight (and preferably of up to 1 mg/kg) is received, given in divided doses as necessary, the precise amount of compound (or salt) administered and the route and form of administration depending on size, age and sex of the person being treated and on the particular disease or medical condition being treated according to principles well known in the medical arts.

[0042] In addition to their aforesaid use in therapeutic medicine in humans, the compounds of formula Ia are also useful in the veterinary treatment of similar conditions affecting commercially valuable warm-blooded animals, such as dogs, cats, horses and cattle. In general for such treatment, the compounds of the formula Ia will be administered in an analogous amount and manner to those described above for administration to humans. The compounds of formula Ia are also of value as pharmacological tools in the development and standardisation of test systems for the evaluation of the effects of endothelin in laboratory animals such as cats, dogs, rabbits, monkeys, rats and mice, as part of the continuing search for new and improved therapeutic agents.

[0043] The invention will now be illustrated by the following non-limiting Examples in which, unless otherwise stated:-

(i) concentrations and evaporations were carried out by rotary evaporation in vacuo;
(ii) operations were carried out at room temperature, that is in the range 18-26°C;
(iii) flash column chromatography was performed on Merck Kieselgel 60 (Art. no. 9385) obtained from E Merck, Darmstadt, Germany;
(iv) where a silica gel Mega Bond Elut column is referred to, this means a column containing 10 g of silica of 40 micron particle size, the silica being contained in a 60 ml disposable syringe and supported by a porous disc, obtained from Varian, Harbor City, California, USA under the name "Mega Bond Elut SI"; and
(iv) yields, where given, are intended for the assistance of the reader only and are not necessarily the maximum attainable by diligent process development.

EXAMPLE 1

[0044] A solution of 5-dimethylamino-1-naphthalenesulphonyl chloride (1.35 g), 2-amino-5-chloropyridine (0.64 g), pyridine (0.40 g) and 4-dimethylaminopyridine (20 mg) in dichloromethane (20 ml) was left to stand for 3 days. The solution was divided into two equal portions and each portion was applied to a silica gel Mega Bond Elut column. The columns were eluted with dichloromethane and the appropriate fractions were concentrated by evaporation. The residue was triturated with ether to give **5-(dimethylamino)-N-(5-chloro-2-pyridyl)-1-naphthalenesulphonamide** (0.77 g), m.p. 160-162°C; mass spectrum [positive fast atom bombardment (+ve FAB), methanol/m-nitrobenzyl alcohol (NBA)]: 362 $(M+H)^+$.

EXAMPLES 2-3

[0045] Using an analogous procedure to that described in Example 1, but starting from the appropriate aminopyridine of formula II, the following compounds of formula I were obtained:-

(Example 2):

[0046] **5-(Dimethylamino)-N-(5-methyl-2-pyridyl)-1-naphthalene-sulphonamide,** m.p. 209-211°C; mass spectrum [positive chemical ionisation (+ve CI)]: 342 $(M+H)^+$; starting from 2-amino-5-methylpyridine; and

(Example 3):

[0047] **5-(Dimethylamino)-N-(5-bromo-2-pyridyl)-1-naphthalene-sulphonamide,** m.p. 176-177°C; mass spectrum (+ve FAB, methanol/NBA): 406 $(M+H)^+$; starting from 2-amino-5-bromopyridine.

EXAMPLE 4

[0048] Oil-free sodium hydride (48 mg) was added to a solution of 2-amino-3,5-dichloropyridine (326 mg) in 1,2-dimethoxyethane (20 ml). After evolution of hydrogen ceased, 5-dimethylamino-1-naphthalene-sulphonyl chloride (540 mg) was added and the mixture was heated at 75°C for 3 days. Volatile material was removed by evaporation and the residue was purified by flash chromatography. Elution with dichloromethane/hexane (3:2 v/v) and trituration of the resulting foam with ether/hexane (1:10 v/v) gave **5-(dimethylamino)-N-(3,5-dichloro-2-pyridyl)-1-naphthalenesulphonamide** (52 mg), m.p. 161-163°C; mass spectrum [+ve FAB, dimethylsulphoxide (DMSO)/glycerol (GLY)]: 396 $(M+H)^+$.

EXAMPLE 5

[0049] Sodium hydride (60% dispersion in oil; 160 mg) was added to a solution of 5-dimethylamino-1-naphthalenesulphonamide (500 mg) in N,N-dimethylformamide (30 ml). When evolution of hydrogen ceased, 2-chloro-5-nitropyridine (317 mg) was added and the solution was heated at 95°C for 18 hours. Volatile material was removed by evaporation and water (50 ml) was added to the residue. The mixture was extracted with ethyl acetate (20 ml), and the aqueous layer was neutralised with 0.05 M aqueous acetic acid (40 ml) and extracted with ethyl acetate (3 x 25 ml). The extracts were washed with water (20 ml) and saturated sodium chloride solution (20 ml) and dried ($MgSO_4$). Volatile material was removed by evaporation and the residue was purified by elution with dichloromethane through a silica gel Mega Bond Elut column. The resulting foam was triturated with ether/hexane (1:1 v/v) to give **5-(dimethylamino)-N-(5-nitro-2-pyridyl)-1-naphthalenesulphonamide** (60 mg), m.p. 196°C; mass spectrum (+ve FAB, methanol/NBA): 373 $(M+H)^+$.

EXAMPLE 6

[0050] A solution of 5-dimethylamino-1-naphthalenesulphonyl chloride (269.5 mg), 2-amino-5-bromo-3-methylpyridine (187 mg) and 4-dimethylaminopyridine (100 mg) in pyridine (5 ml) was heated at 85°C for 18 hours. Volatile material was removed by evaporation and dichloromethane (50 ml) was added. Insoluble material was removed by filtration and the filtrate was concentrated by evaporation. The residue was purified by flash chromatography, eluting with ethyl acetate/hexane (1:1 v/v), to give **5-(dimethylamino)-N-(5-bromo-3-methyl-2-pyridyl)-1-naphthalenesulphonamide** as a foam (135 mg); NMR ($CDCl_3$): 2.2(s, 3H), 2.9(s, 6H), 7.15(d, 1H), 7.4-7.8(m, 4H), 8.4(d, 1H), 8.5(d, 2H); mass spectrum (+ve CI): 420 $(M+H)^+$.

EXAMPLE 7

[0051] Using an analogous procedure to that described in Example 6, but using a proportionate amount of 2-amino-5-trifluoromethylpyridine in place of 2-amino-5-bromo-3-methylpyridine, there was thus obtained **5-(dimethylamino)-N-(5-trifluoromethyl-2-pyridyl)-1-naphthalenesulphonamide,** m.p. 185-186°C; mass spectrum (+ve FAB, DMSO/methanol/NBA): 396 $(M+H)^+$.

EXAMPLE 8

[0052] Using an analogous procedure to that described in Example 6, but using a proportionate amount of 2-amino-5-iodopyridine in place of 2-amino-5-bromo-3-methylpyridine and carrying out the reaction at ambient temperature, there was thus obtained **5-(dimethylamino)-N-(5-iodo-2-pyridyl)-1-naphthalenesulphonamide**, m.p. 211-212°C; mass spectrum (+ve FAB, DMSO/GLY): 454$(M+H)^+$.

EXAMPLE 9

[0053] Using an analogous procedure to that described in Example 1, but using a proportionate amount of 6-amino-3-bromo-2-methylpyridine in place of 2-amino-5-chloropyridine, there was thus obtained **5-(dimethylamino)-N-(5-bromo-6-methyl-2-pyridyl)-1-naphthalene-sulphonamide,** m.p. 155-156°C; mass spectrum (+ve CI): 420 $(M+H)^+$.

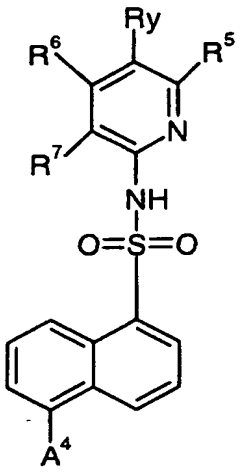
EXAMPLE 10 (Note: all parts by weight)

[0054] The compounds of the invention may be administered for therapeutic or prophylactic use to warm-blooded animals such as man in the form of conventional pharmaceutical compositions, typical examples of which include the following:-

a) **Capsule** (for oral administration)	
Active ingredient *	20
Lactose powder	578.5
Magnesium stearate	1.5
b) **Tablet** (for oral administration)	
Active ingredient *	50
Microcrystalline cellulose	400
Starch (pregelatinised)	47.5
Magnesium stearate	2.5
c) **Injectable Solution** (for intravenous administration)	
Active ingredient *	0.05 - 1.0
Propylene glycol	5.0
Polyethylene glycol (300)	3.0 - 5.0
Purified water	to 100%
d) **Injectable Suspension** (for intramuscular administration)	
Active ingredient *	0.05 - 1.0
Methylcellulose	0.5
Tween 80	0.05
Benzyl alcohol	0.9
Benzalkonium chloride	0.1
Purified water	to 100%
Note: the active ingredient * may typically be an Example described hereinbefore or as a pharmaceutically acceptable salt. Tablets and capsules formulations may be coated in conventional manner in order to modify or sustain dissolution of the active ingredient. Thus, for example, they may be coated with a conventional enterically digestible coating.	

Claims

1. A compound of the formula Ia



Ia

wherein Ry is selected from halogeno, (1-4C)alkyl, trifluoromethyl and nitro; A^4 is selected from:-

(i) (1-4C)alkanoylamino;
(ii) the group -NRaRb in which Ra and Rb are the same and are selected from methyl, ethyl and propyl;
(iii) the group -NRaRb in which one of Ra and Rb is methyl and the other is ethyl or propyl; and
(iv) the group -NRaRb in which one of Ra and Rb is hydrogen and the other is methyl, ethyl, propyl, isopropyl, isobutyl or sec-butyl; and R^5, R^6 and R^7 are independently selected from hydrogen, halogeno, (1-4C)alkoxy and (1-4C)alkyl; or a pharmaceutically-acceptable salt thereof.

2. A compound as claimed in claim 1 in which A^4 is 5-dimethylamino.

3. A compound as claimed in claim 1 or 2 in which Ry is halogeno.

4. A compound as claimed in claim 1, 2 or 3 in which R^5, R^6 and R^7 are independently selected from hydrogen, methyl, chloro and bromo.

5. A compound of the formula Ia as claimed in claim 1 selected from:

5-(dimethylamino)-N-(5-chloro-2-pyridyl)-1-naphthalenesulphonamide;
5-(dimethylamino)-N-(5-bromo-2-pyridyl)-1-naphthalenesulphonamide;
5-(dimethylamino)-N-(5-bromo-3-methyl-2-pyridyl)-1-naphthalenesulphonamide; and
5-(dimethylamino)-N-(5-trifluoromethyl-2-pyridyl)-1-naphthalenesulphonamide;

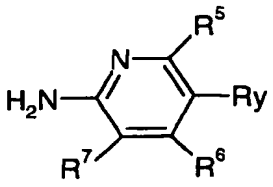
or a pharmaceutically-acceptable salt thereof.

6. A salt as claimed in any one preceding claim which is selected from salts with bases forming physiologically acceptable cations and, for those compounds which are sufficiently basic, salts with acids forming physiologically acceptable anions.

7. A pharmaceutical composition which comprises a compound of the formula Ia or a pharmaceutically-acceptable salt thereof, as claimed in any of claims 1 to 6, together with a pharmaceutically-acceptable diluent or carrier.

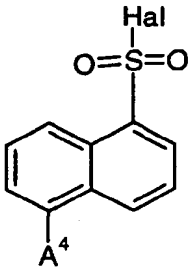
8. A process for the manufacture of a compound of formula Ia as claimed in claim 1, or a pharmaceutically-acceptable salt thereof, which is characterised in that:-

(a) an amine of the formula II



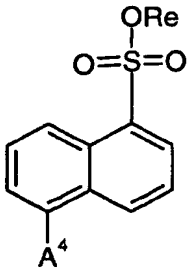
II

or an alkali metal salt thereof, is reacted with a sulphonyl halide of formula III



III

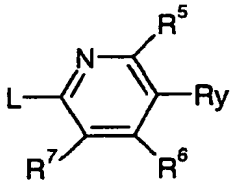
in which Hal. is a halogeno group or with a sulphonate of the formula IIIa



IIIa

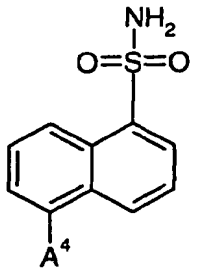
in which Re is an electron deficient phenyl group; or

(b) a compound of formula IV



IV

in which L is a leaving group is reacted with a sulphonamide of the formula V



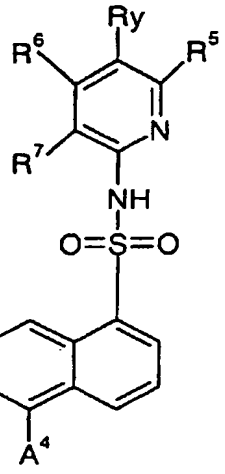
V

or an alkali metal salt thereof;
whereafter a compound of the formula Ia may be converted into another compound of formula Ia by conventional functional group interconversion;
whereafter a protecting group, if present, may be removed;
whereafter when a pharmaceutically-acceptable salt of a compound of formula Ia is required, it is required, it is obtained by reaction with the appropriate acid or base affording a physiologically-acceptable ion, or by any other conventional salt formation procedure;
whereafter when an optically active form of a compound of formula Ia is required, one of the aforesaid processes (a)-(b) may be carried out using an optically active starting material, or the racemic form of a compound of formula Ia is resolved;
and wherein A^4, Ry, R^5, R^6 and R^7 have any of the meanings defined in any of claims 1-4 unless otherwise stated.

9. The use of a compound of the formula Ia as claimed in claim 1, or a pharmaceutically-acceptable salt thereof, for the manufacture of a medicament for use in the treatment of a disease or condition where elevated or abnormal levels of endothelin play a significant causative role.

Patentansprüche

1. Verbindungen der Formel Ia



Ia

wobei Ry unter Halogen, (1-4C)Alkyl, Trifluormethyl und Nitro ausgewählt ist; A^4 unter den folgenden Gruppen ausgewählt ist:

(i) (1-4C)Alkanoylamino;
(ii) der Gruppe -NRaRb, in welcher Ra und Rb gleich und unter Methyl, Ethyl und Propyl ausgewählt sind;
(iii) der Gruppe- NRaRb, in welcher einer der Reste Ra und Rb für Methyl und der andere für Ethyl oder Propyl steht; und
(iv) der Gruppe -NRaRb, in welcher einer der Reste Ra und Rb für Wasserstoff und der andere für Methyl, Ethyl, Propyl, Isopropyl, Isobutyl oder sec-Butyl steht; und R^5, R^6 und R^7 unabhängig unter Wasserstoff, Halogen, (1-4C) Alkoxy und (1-4C) Alkyl ausgewahlt sind;
oder ein pharmazeutisch verträgliches Salz davon.

2. Verbindungen nach Anspruch 1, in denen A^4 für 5-Dimethylamino steht.

3. Verbindungen nach Anspruch 1 oder 2, in denen Ry für Halogen steht.

4. Verbindungen nach Anspruch 1, 2 oder 3, in denen R^5, R^6 und R^7 unabhängig unter Wasserstoff, Methyl, Chlor und Brom ausgewählt sind.

5. Verbindungen der Formel Ia nach Anspruch 1 ausgewählt unter:

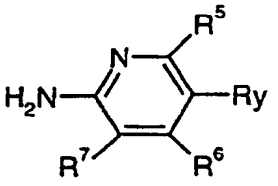
5-(Dimethylamino)-N-(5-chlor-2-pyridyl)-1-naphthalinsulfonamid;
5-(Dimethylamino)-N-(5-brom-2-pyridyl)-1-naphthalinsulfonamid;
5-(Dimethylamino)-N-(5-brom-3-methyl-2-pyridyl)-1-naphthalisulfonamid; und
5-(Dimethylamino)-N-(5-trifluormethyl-2-pyridyl)-1-naphthalisulfonamid;
oder pharmazeutisch verträgliche Salze davon.

6. Salze nach einem der vorhergehenden Ansprüche, ausgewählt unter Salzen mit Basen, die physiologisch verträgliche Kationen bilden, und im Fall von Verbindungen, die ausreichend basisch sind, Salzen mit Säuren, die physiologisch verträgliche Anionen bilden.

7. Pharmazeutische Zusammensetzungen, enthaltend eine Verbindung der Formel Ia oder ein pharmazeutisch verträgliches Salz davon nach einem der Ansprüche 1 bis 6, zusammen mit einem pharmazeutisch verträglichen Verdünnungsmittel oder Träger.

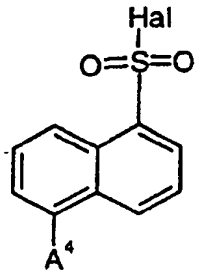
8. Verfahren zur Herstellung einer Verbindung der Formel Ia nach Anspruch 1 oder eines pharmazeutisch verträglichen Salzes davon, dadurch gekennzeichnet, daß man

(a) ein Amin der Formel II



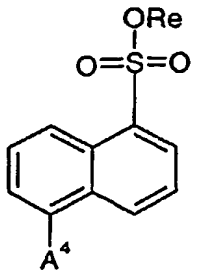
II

oder ein Alkalisalz davon mit einem Sulfonsäurehalogenid der Formel III



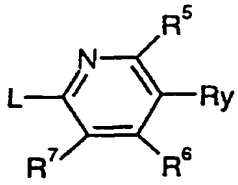
III

in welcher Hal für eine Halogengruppe steht oder mit einem Sulfonat der Formel IIIa



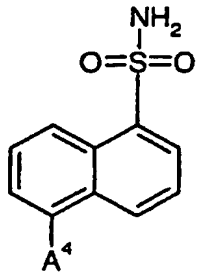
IIIa

in welcher Re für eine elektronenarme Phenylgruppe steht, umsetzt; oder
(b) eine Verbindung der Formel IV



IV

in welcher L für eine Abgangsgruppe steht, mit einem Sulfonamid der Formel V



V

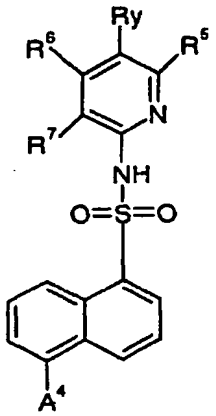
oder einem Alkalisalz davon umsetzt;
worauf man eine Verbindung der Formel Ia durch übliche Umwandlung von funktionellen Gruppen in eine andere Verbindung der Formel Ia umwandeln kann;

worauf man eine Schutzgruppe, falls vorhanden, entfernen kann;
worauf man, wenn man ein pharmazeutisch verträgliches Salz einer Verbindung der Formel Ia benötigt, dieses durch Umsetzung mit der geeigneten Säure oder Base, welche ein physiologisch verträgliches Ion liefert, oder durch irgendein anderes übliches Verfahren zur Bildung von Salzen erhält;
worauf man, wenn man eine optisch aktive Form einer Verbindung der Formel Ia benötigt, eines der oben genannten Verfahren (a) - (b) unter Verwendung eines optisch aktiven Ausgangsmaterials durchführt, oder das Racemat einer Verbindung der Formel Ia spaltet;
und wobei A^4, Ry, R^5, R^6 und R^7 eine der in einem der Ansprüche 1-4 definierten Bedeutungen haben, wenn nicht anders angegeben.

9. Verwendung einer Verbindung der Formel Ia nach Anspruch 1 oder eines pharmazeutisch verträglichen Salzes davon für die Herstellung eines Medikaments zur Verwendung bei der Behandlung einer Erkrankung oder eines Zustandes, bei dem erhöhte oder anormale Endothelinkonzentrationen eine signifikante kausale Rolle spielen.

Revendications

1. Composé de formule Ia



Ia

dans lequel Ry est sélectionné parmi un halogène, un alkyle de 1-4 C, un trifluorométhyle et un nitro; A^4 est sélectionné parmi :

(i) un (alcanoyl de 1-4 C)amino;
(ii) le groupement -NRaRb dans lequel Ra et Rb sont identiques et sont sélectionnés parmi un méthyle, un éthyle et un propyle;
(iii) le groupement -NRaRb dans lequel un parmi Ra et Rb est un méthyle et l'autre est un éthyle ou un propyle, et
(iv) le groupement -NRaRb dans lequel un parmi Ra et Rb est un hydrogène et l'autre est un méthyle, un éthyle, un propyle, un i-propyle, un i-butyle ou un sec-butyle, et R^5, R^6 et R^7 sont indépendamment sélectionnés parmi un hydrogène, un halogène, un alcoxy de 1-4 C, un alkyle de 1-4 C; ou un sel pharmaceutiquement acceptable de ceux-ci.

2. Composé suivant la revendication 1, dans lequel A^4 est le 5-diméthylamino.

3. Composé suivant la revendication 1 ou 2, dans lequel Ry est un halogène.

4. Composé suivant la revendication 1, 2 ou 3, dans lequel R^5, R^6 et R^7 sont indépendamment sélectionnés parmi un hydrogène, un méthyle, un chlore et un brome.

5. Composé de formule Ia suivant la revendication 1, sélectionné parmi :

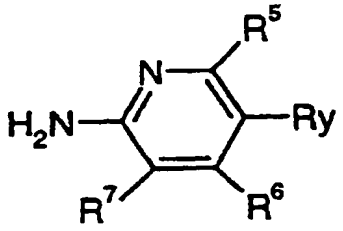
le 5-(diméthylamino)-N-(5-chloro-2-pyridyl)-1-naphtalènesulfonamide; le 5-(diméthylamino)-N-(5-bromo-2-pyridyl)-1-naphtalènesulfonamide; le 5-(diméthylamino)-N-(5-bromo-3-méthyl-2-pyridyl)-1-naphtalènesulfonamide; et le 5-(diméthylamino)-N-(5-trifluorométhyl-2-pyridyl)-1-naphtalène-sulfonamide; ou un sel pharmaceutiquement acceptable de ceux-ci.

6. Sel suivant l'une quelconque des revendications précédentes, qui est sélectionné parmi des sels avec des bases formant des cations physiologiquement acceptables et, pour les composés qui sont suffisamment basiques, des sels avec des acides formant des anions physiologiquement acceptables.

7. Composition pharmaceutique qui comprend un composé de formule Ia ou un sel pharmaceutiquement acceptable de celui-ci, suivant l'une quelconque des revendications 1 à 6, conjointement avec un diluant ou un véhicule pharmaceutiquement acceptable.

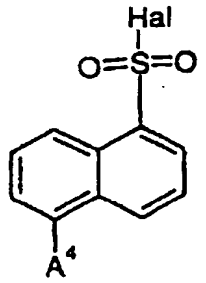
8. Procédé de fabrication d'un composé de formule Ia suivant la revendication 1, ou un sel pharmaceutiquement acceptable de celui-ci, qui est caractérisé en ce que :

(a) une amine de formule II



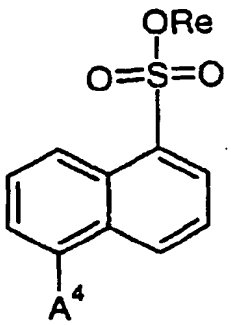
II

ou un sel de métal alcalin de celle-ci, est mise à réagir avec un halogénure de sulfonyle de formule III



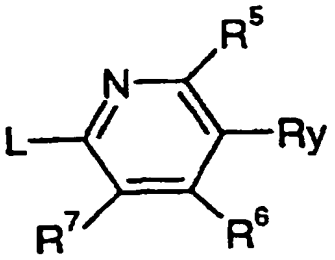
III

dans lequel Hal, est un groupement halogéno ou avec un sulfonate de formule IIIa



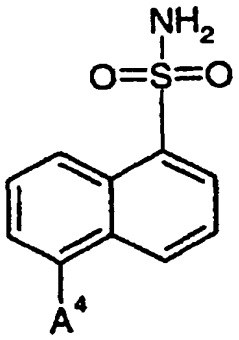
IIIa

dans lequel Re est un groupement phényle pauvre en électrons; ou
(b) un composé de formule IV



IV

dans lequel L est un groupement sortant est mis à réagir avec un sulfonamide de formule V



V

ou un sel de métal alcalin de celui-ci;
après quoi, un composé de formule Ia peut être converti en un autre composé de formule Ia par échange réciproque classique de groupements fonctionnels;
après quoi, un groupement de protection, s'il y en a, peut être enlevé;
après quoi, lorsqu'un sel pharmaceutiquement acceptable d'un composé de formule Ia est requis, il est obtenu par réaction avec l'acide approprié ou la base appropriée donnant un ion physiologiquement acceptable, ou par un quelconque autre procédé classique de formation de sel;
après quoi, lorsqu'une forme optiquement active d'un composé de formule Ia est requise, un des procédés susmentionnés (a)-(b) peut être réalisé en utilisant un matériau de départ optiquement actif, ou la forme racémique d'un composé de formule Ia est résolue;
et dans lequel A^4, Ry, R^5, R^6 et R^7 ont une quelconque des significations définies dans l'une quelconque des revendications 1-4 sauf indication contraire.

9. Utilisation d'un composé de formule Ia suivant la revendication 1, ou d'un sel pharmaceutiquement acceptable de celui-ci, pour la fabrication d'un médicament pour une utilisation dans le traitement d'une maladie ou d'un trouble où des taux élevés ou anormaux d'endothéline jouent un rôle causal significatif.